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RAnoLazIne for the Treatment of Diastolic Heart Failure in Patients With Preserved Ejection Fraction

The RALI-DHF Proof-of-Concept Study

Lars S. Maier, MD,* Beth Layug, MD,† Ewa Karwatowska-Prokopczuk, MD, PhD,† Luiz Belardinelli, MD,† Stella Lee, MS,† Julia Sander, MS,* Christian Lang, MS,* Rolf Wachter, MD,* Frank Edelmann, MD,* Gerd Hasenfuss, MD,* Claudius Jacobshagen, MD*

Göttingen, Germany; and Foster City, California

Objectives This study investigated whether inhibiting late Na^+ current by using ranolazine improved diastolic function in patients with heart failure with preserved ejection fraction (HFpEF).

Background HFpEF accounts for >50% of all HF patients, but no specific treatment exists.

Methods The RALI-DHF (RAnoLazIne for the Treatment of Diastolic Heart Failure) study was a prospective, randomized, double-blind, placebo-controlled small proof-of-concept study. Inclusion criteria were EF ≥45%, a mitral E-wave velocity/mitral annular velocity ratio (E/E′) >15 or N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentration >220 pg/ml, a left ventricular end-diastolic pressure (LVEDP) ≥18 mm Hg, and time-constant of relaxation (tau) ≥50 ms. Patients were randomized to ranolazine (n = 12) or placebo (n = 8). Treatment consisted of intravenous infusion for 24 h, followed by oral treatment for 13 days.

Results After 30 min of infusion, LVEDP (p = 0.04) and pulmonary capillary wedge pressure (p = 0.04) decreased in the ranolazine group but not in the placebo group. Mean pulmonary artery pressure showed a trend toward a decrease in the ranolazine group that was significant under pacing conditions at 120 beats/min (p = 0.02), but not for the placebo group. These changes occurred without changes in left ventricular end-systolic pressure or systemic or pulmonary resistance but in the presence of a small but significant decrease in cardiac output (p = 0.04). Relaxation parameters (e.g., tau, rate of decline of left ventricular pressure per minute [dP/dt_{min}]) were unaltered. Echocardiographically, the E/E′ ratio did not significantly change after 22 h. After 14 days of treatment, no significant changes were observed in echocardiographic or cardiopulmonary exercise test parameters. There were no significant effects on NT-pro-BNP levels.

Conclusions Results of this proof-of-concept study revealed that ranolazine improved measures of hemodynamics but that there was no improvement in relaxation parameters. (Ranolazine in Diastolic Heart Failure [RALI-DHF]; NCT01163734) (J Am Coll Cardiol HF 2013;1:115–22) © 2013 by the American College of Cardiology Foundation

Approximately half of the patients with heart failure (HF) have diastolic HF, often referred to as HF with preserved ejection fraction (HFpEF) (1–3). The prognosis of HFpEF is comparable to that of systolic heart failure (SHF) with a 5-year mortality rate of ~50% (1,3–5). Whereas a variety of evidence-based therapies exist for the improvement of symptoms and prognosis for SHF patients, treatment options for HFpEF patients are limited (1,6–8). To date, there is no evidence-based treatment for HFpEF patients, and most clinical trials using pharmacological agents have failed (6,9–11). Recently, exercise training has been shown to improve left ventricular diastolic function, exercise capacity, and quality of life (12).

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In patients with end-stage HF, late Na^+ current (I_{Na}) is increased in cardiac myocytes, leading to elevated intracellular Na^+ levels and Ca^{2+} overload (13–15). This raises diastolic tone of the heart, contributing to diastolic dysfunction. By inhibiting late I_{Na} using ranolazine, Na^+ accumulation can be decreased (15,16). Hence, ranolazine would

From the *Department of Cardiology and Pneumology, Georg-August-University, Göttingen, Germany; and †Gilead Sciences, Inc., Foster City, California. This study was funded by Gilead Sciences, Inc. Dr. Maier was funded by Deutsche Forschungsgemeinschaft (DFG) (MA1982/4-2, TPA03 SFB 1002) and Fondation Leducq as well as by the DZHK (Deutsches Zentrum für Herz-Kreislauf-Forschung). Dr. Maier received research grants from Gilead, Inc.; and serves as consultant with Berlin-Chemie. Drs. Jacobshagen, Wachter, and Edelmann have received honoraria from Berlin-Chemie. Drs. Layug, Karwatowska-Prokopczuk, Belardinelli, and Lee are employees of Gilead, Inc.

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Abbreviations and Acronyms

CPET = cardiopulmonary exercise test
DHF = diastolic heart failure
E/E′ = mitral E wave velocity/mitral annular velocity ratio
ECG = electrocardiogram
ECHO = echocardiography
EF = ejection fraction
HF = heart failure
IV = intravenous
late I_{Na} = late Na^+-current
LVEDP = left ventricular end-diastolic pressure
NT-proBNP = N-terminal pro-B-type natriuretic peptide
NYHA = New York Heart Association
PAP = pulmonary artery pressure
PCWP = pulmonary capillary wedge pressure
PH = pulmonary hypertension
PVR = pulmonary vascular resistance
SHF = systolic heart failure
SVR = systemic vascular resistance
Tau = time constant for relaxation

be expected to promote Ca^{2+} extrusion through the Na^+/Ca^{2+} exchanger and thereby improve diastolic tension and relaxation. Data from a HF dog model indicate that ranolazine improves diastolic function (e.g., in left ventricular end-diastolic pressure [LVEDP]) as a parameter for diastolic dysfunction (17). Furthermore, ranolazine has been shown to improve diastolic function in patients with coronary artery disease (18,19).

The objective of this proof-of-concept trial was to determine whether ranolazine improves diastolic function in HFpEF patients.

Methods

Study design. The RALI-DHF (RAnoLazIne for the Treatment of Diastolic Heart Failure) study was a prospective, single-center, randomized, double-blind, placebo-controlled proof-of-concept study (NCT01163734, EudraCT 2009-017168-17).

Patients with symptoms of HF (New York Heart Association [NYHA] class II to III) were screened for inclusion in the study. Inclusion criteria consisted of left ventricular ejection fraction (LVEF) ≥45%, a mitral E-wave velocity/mitral annular velocity ratio (E/E′) >15 or an N-terminal pro–B-type natriuretic peptide (NT-pro-BNP) concentration >220 pg/ml at screening, and as continued eligibility criteria, an average resting LVEDP ≥18 mm Hg, as well as resting time constant of relaxation (tau) ≥50 ms during cardiac catheterization (2,9).

Study conduct and procedures. The study consisted of an intravenous bolus injection and continuous infusion of ranolazine or placebo for 24 h. One hour prior to the end of the 24-h infusion, patients were started on an oral study drug regimen, 1,000 mg twice daily, which they continued for 13 days (Fig. 1A).

Invasive hemodynamic measurements were performed initially, before the first intravenous bolus of study drugs. Pacing was performed at 120 beats/min for better comparison among patients, and hemodynamic and pressure measurements were collected again (20). These measurements were repeated 30 min after the initial intravenous bolus administration under both resting and paced conditions for two reasons: first, the goal was to further impair diastolic filling, and second, we wanted to exclude differences in heart rate as a confounder.

Tissue Doppler echocardiography and 12-lead electrocardiography were performed before catheterization, repeated 60 min prior to administration of oral study drug, and at day 14. Cardiopulmonary exercise test (CPET) was performed at baseline and on day 14.

Endpoints. Exploratory endpoints were 1) changes from baseline to 30 min in hemodynamic parameters under resting and paced conditions, including LVEDP, rate of decline of left ventricular pressure per minute (dP/dt_{min}), and tau (20); and 2) changes from baseline to day 14 in echocardiographic parameters including E/E′, CPET parameters including oxygen consumption (Vo_{2max}), and NT-pro-BNP.

Statistical considerations. Between-treatment comparisons of all exploratory efficacy endpoints were analyzed using the Wilcoxon rank sum test. Within-treatment comparisons were analyzed using the Wilcoxon signed rank test. Values are mean ± SEM. A detailed Methods section can be found in the Online Appendix.

Results

Baseline characteristics. Twenty patients received the study drug and completed the trial (Fig. 1B). Table 1 summarizes baseline patient characteristics, which were comparable among patients between the groups. Basal functional parameters (Table 2) showed severe diastolic dysfunction in the presence of unaltered systolic left ventricular function.

Hemodynamics. Table 3 shows hemodynamic data during resting conditions. After 30 min, LVEDP decreased significantly in the ranolazine group (from 21.3 ± 1.0 mm Hg to 19.1 ± 1.7 mm Hg, $p = 0.04$) but not in the placebo group (Fig. 2A). Most of the patients in the ranolazine group showed a decrease in LVEDP (Fig. 2B). A comparison of the two groups showed no significant differences. Pulmonary capillary wedge pressure (PCWP) significantly decreased in the ranolazine group (from 14.3 ± 1.9 mm Hg to 12.2 ± 1.9 mm Hg, $p = 0.04$) but with a modest difference compared to that in the placebo group ($p = 0.05$) (Fig. 3A). Individual results underline the average data (Fig. 3B). Mean pulmonary artery pressure (mPAP) showed a nonsignificant decrease in the ranolazine group (Fig. 4A) that was statistically significant under pacing conditions (from 26.5 ± 2.7 to 25.2 ± 2.5, $p = 0.02$), without changes for the placebo group (Fig. 4B, Online Table).

These changes occurred without decreases in left ventricular end-systolic pressure or systemic or pulmonary resistance in the ranolazine group. Interestingly, there were no changes with respect to relaxation kinetics (e.g., tau, dP/dt_{min}) (Table 3).

Cardiac output at rest decreased in the ranolazine group (from 4.3 ± 0.2 l/min to 4.0 ± 0.2 l/min; $p = 0.04$) but not in the placebo group. This effect was more pronounced under pacing conditions ($p < 0.01$) (Online Table). Similarly, dP/dt_{max} decreased from 2,024.1 ± 167.7 mm Hg/s to 1,706.2 ± 74.3 mm Hg/s ($p = 0.01$) and stroke volume

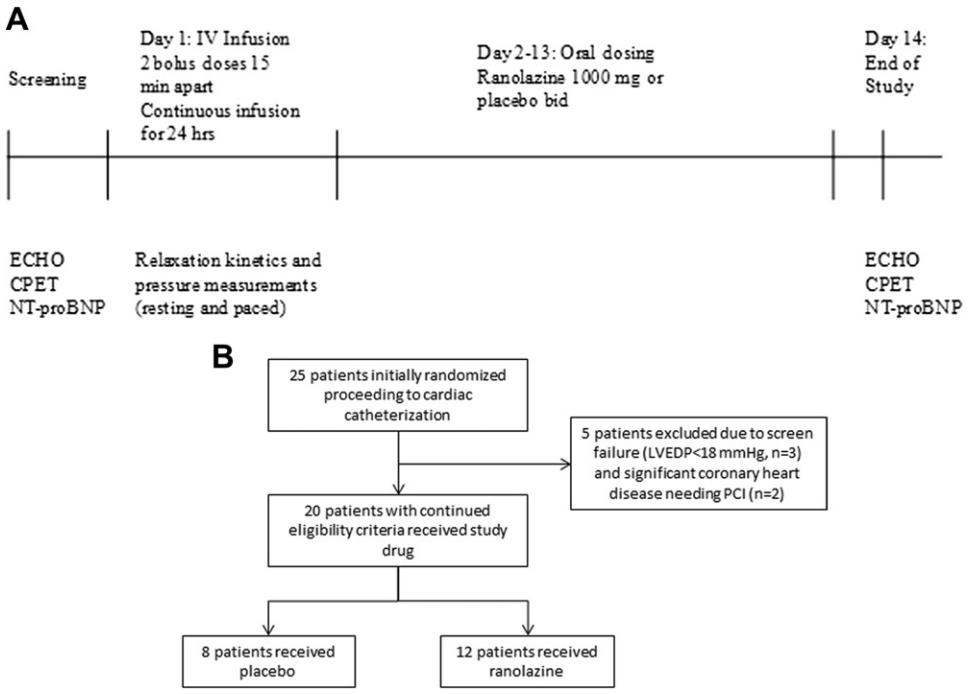

Figure 1 Schematic Overview

(A) Schematic overview of the study protocol. **(B)** Flowchart of patients screened and included in the study. CPET = cardiopulmonary exercise test; ECHO = echocardiography; IV = intravenous; LVEDP = left ventricular end-diastolic pressure; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PCI = percutaneous coronary intervention.

Table 1 Patient Baseline Characteristics

Baseline Characteristic	Placebo	Ranolazine	p Value
Age (yrs)	73.1 ± 2.3	70.4 ± 2.2	0.485
BMI (kg/m^2)	33.5 ± 5.1	29.2 ± 1.3	0.787
Body weight (kg)	91.0 ± 16.4	79.6 ± 4.0	0.816
Females/males	6/2	10/2	1.000
NYHA functional class II	3 (37.5%)	5 (41.7%)	1.000
NYHA functional class III	5 (62.5%)	7 (58.3%)	1.000
Hypertension	8 (100%)	12 (100%)	NA
Diabetes mellitus	4 (50%)	3 (25%)	0.356
Dyslipidemia	5 (62.5%)	9 (75%)	0.642
Supraventricular/ventricular arrhythmia	3 (37.5%)	3 (25%)	0.642
Previous MI/angina pectoris	3 (37.5%)	4 (33.3%)	1.000
PCI/CABG	2 (25%)	3 (25%)	1.000
Peripheral vascular disease	0	1 (8.3%)	1.000
Asthma/COPD	3 (37.5%)	2 (16.7%)	0.347
Concomitant medications			
ACE inhibitors/ARBs	8 (100%)	12 (100%)	NA
Beta-blockers	6 (75%)	10 (83%)	1.000
Dihydropyridine derivatives	4 (50%)	3 (25%)	0.356
Statins	3 (37%)	7 (58%)	0.410
Acetylsalicylic acid	7 (87%)	9 (75%)	0.619
Nitrates	1 (12%)	2 (17%)	1.000

Values are mean ± SEM, n, or n (%). Wilcoxon rank sum test was used for continuous variables, and Fisher's exact test was used for the other variables.

ACE = angiotensin receptor blocker; ARB = angiotensin receptor blockers; BMI = body mass index; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; MI = myocardial infarction; NA = not available; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

from 42.4 ± 2.1 ml to 37.5 ± 2.3 ml ($p < 0.01$) (Online Table) without changes in the placebo group under pacing conditions.

Cardiopulmonary exercise test. Table 4 shows CPET parameters at baseline and after 14 days. There were no significant changes between placebo and ranolazine parameters.

Table 2 Basal Functional Parameters

Baseline Parameters	Placebo (n = 8)	Ranolazine (n = 12)	p Value
LVEDP (mm Hg)	23.1 ± 2.6	21.3 ± 1.0	0.728
PCWP (mm Hg)	17.0 ± 3.0	14.3 ± 1.9	0.418
mPAP (mm Hg)	28.7 ± 3.5	24.4 ± 2.4	0.164
Tau (ms)	62 ± 2	59 ± 3	0.190
Ejection fraction (%)	59 ± 1	66 ± 2	0.027
E/E′	18.3 ± 2.3	19.1 ± 1.0	0.908
NT-proBNP (pg/ml)	846 ± 355	708 ± 389	0.386
Peak Vo_2 (ml/kg/min)	9.0 ± 1.7	11.8 ± 1.5	0.008
CPET Exercise duration (s)	225 ± 35	398 ± 66	0.057
VE/VCo_2	36.0 ± 5.1	35.4 ± 2.1	0.471
Creatinine (mg/dl)	1.09 ± 0.15	0.98 ± 0.10	0.698
Creatinine clearance (ml/min)	68.8 ± 11.9	74.2 ± 10.0	0.058

Values are mean ± SEM. Wilcoxon rank sum test was used.

CPET = cardiopulmonary exercise test; E/E′ = mitral E-wave velocity/mitral annular velocity; LVEDP = left ventricular end-diastolic pressure; mPAP = mean pulmonary arterial pressure; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PCWP = pulmonary capillary wedge pressure; tau = time constant for relaxation; VE/VCo_2 = exercise ventilation/carbon dioxide production ratio.

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Table 3 Hemodynamic Parameters

Parameter	Placebo			Ranolazine			p Value
	Baseline	30 min	p Value	Baseline	30 min	p Value	Plac vs Ran
LVEDP (mm Hg)	23.1 ± 2.6	22.5 ± 2.6	0.92	21.3 ± 1.0	19.1 ± 1.7	0.04	0.11
LVESP (mm Hg)	138.3 ± 12.3	150.5 ± 11.7	<0.01	148.4 ± 7.9	149.5 ± 6.9	0.83	0.10
PCWP (mm Hg)	17.0 ± 3.0	18.0 ± 4.0	0.70	14.3 ± 1.9	12.2 ± 1.9	0.04	0.05
mPAP (mm Hg)	28.7 ± 3.5	29.2 ± 4.4	0.97	24.4 ± 2.4	22.2 ± 2.6	0.08	0.13
sPAP (mm Hg)	41.5 ± 5.2	41.8 ± 6.4	1.00	36.4 ± 3.7	34.6 ± 4.0	0.33	0.28
dP/dt min (mm Hg/s)	−1,738.2 ± 123.5	−1,884.0 ± 146.0	0.04	−1,986.1 ± 94.5	−1,982.5 ± 100.7	0.91	0.15
Tau (ms)	62.3 ± 2.6	62.4 ± 2.6	0.74	59.39 ± 3.2	62.2 ± 3.9	0.06	0.11
t relax (ms)	173.1 ± 14.3	162.7 ± 11.7	0.06	201.8 ± 31.5	181.4 ± 13.9	0.85	0.20
SVR (dyn·s·cm^{-5})	2,174.4 ± 297.3	2,446.7 ± 351.7	0.03	1,798.2 ± 128.9	1,928.0 ± 95.5	0.13	0.22
PVR (dyn·s·cm^{-5})	238.3 ± 43.9	231.9 ± 28.1	0.95	182.9 ± 18.6	197.3 ± 24.0	0.99	0.67
CO (l/min)	4.4 ± 0.7	4.4 ± 0.8	0.64	4.3 ± 0.2	4.0 ± 0.2	0.04	0.30
RA (mm Hg)	8.0 ± 0.8	8.7 ± 1.3	0.63	8.9 ± 0.8	8.2 ± 0.9	0.08	0.16
dP/dt max (mm Hg/s)	1,295.9 ± 85.2	1,342.0 ± 94.7	0.38	1,503.8 ± 126.0	1,463.5 ± 147.0	0.47	0.23
t sys (ms)	273.9 ± 37.8	303.3 ± 33.4	0.15	334.3 ± 15.8	325.7 ± 14.5	0.05	0.03
t sys (%)	30.6 ± 4.5	34.3 ± 3.7	0.22	36.8 ± 1.6	35.6 ± 1.3	0.13	0.04
t dias (ms)	885.8 ± 54.6	858.9 ± 44.5	0.20	890.4 ± 44.3	899.9 ± 41.3	0.42	0.13
Stroke vol (ml)	67.38 ± 10.9	63.3 ± 10.2	0.02	65.4 ± 3.3	62.1 ± 3.0	0.14	0.85

Values are mean ± SEM. p Values compare baseline versus 30-min values.

CO = cardiac output; dP/dt max = rate of rise of left ventricular pressure; dP/dt min = rate of decline of left ventricular pressure; LVEDP = left ventricular end-diastolic pressure; LVESP = left ventricular end-systolic pressure; mPAP = mean pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; Plac vs Ran = comparison of 30-min values between groups ; PVR = pulmonary vascular resistance; RA = right atrial pressure; sPAP = systolic pulmonary arterial pressure; stroke vol = stroke volume; SVR = systemic vascular resistance; t dias = time in diastole; t relax = time for relaxation; t sys = time in systole; tau = time constant for relaxation.

Echocardiographic data. Table 5 shows echocardiographic data at baseline, after 22 h, and after 14 days. There were no significant differences between any of the parameters in either group.

Pharmacokinetic parameters of ranolazine. Mean ranolazine plasma concentrations were 1,610 ng/ml at 10 min, 4,036 ng/ml at 20 min, 3,109 ng/ml at 30 min, and 5,370 ng/ml at 22 h. Based on concentration-time data, the mean minimum ranolazine plasma concentration was 1,610 ± 108 ng/ml, and the peak plasma concentration was 5,595 ± 490 ng/ml.

Laboratory test parameters. NT-pro-BNP values were elevated in both groups but did not change significantly during follow-up. No other laboratory test value showed a significant change during the course of the trial.

Safety parameters and side effects. There were no changes in systolic and diastolic blood pressure or heart rate (Table 6). There were nonsignificant increases in QT and QTc intervals in the ranolazine group but not in the placebo group. No other electrocardiography parameters showed any significant changes. No patient had arrhythmias (Table 7).

Adverse events were experienced by 87.5% of patients in the placebo group and by 83.3% of patients in the ranolazine group (constipation, vertigo, hematoma, nausea, back pain, hypotension, headache). The proportion of patients with constipation was higher in the ranolazine group (58% vs. 0% in the placebo group), whereas all other adverse events were comparable between groups. Three patients (ranolazine group) had serious adverse events: in 2 patients these events were considered related to the cardiac catheterization procedures. One patient experienced severe musculoskeletal pain attributed to a preexisting condition (a previous rib fracture).

Table 4 CPET Parameters

Parameter	Placebo (n = 8)			Ranolazine (n = 11)			p Value
	Baseline	14 Days	p Value	Baseline	14 Days	p Value	Plac vs. Ran
Peak O_2 uptake (ml/kg/min)	6.5 ± 1.4	6.4 ± 0.9	0.98	8.7 ± 1.3	9.4 ± 1.7	0.56	0.93
VE/VCo_2	33.6 ± 3.3	34.4 ± 2.5	1.00	34.2 ± 2.4	30.5 ± 2.1	0.63	0.80
RER	1.1 ± 0.1	1.1 ± 0.0	0.88	1.1 ± 0.1	1.2 ± 0.1	0.03	0.17
Exercise duration (s)	225 ± 35.4	263 ± 27.6	0.19	398 ± 168.8	453 ± 79.8	0.24	0.87
Exercise level at AT (w)	40 ± 6.3	34 ± 5.7	NA	50 ± 5.3	49 ± 6.8	1.00	1.00

Values are mean ± SEM. Peak O_2 uptake is expressed as the change from resting to exercise. One patient who originally received intravenous infusion was erroneously given placebo tablets by the pharmacist and therefore was excluded from all CPET data analysis. p Values compare baseline versus values at 14 days.

Plac vs. Ran = comparison with values at 14 days; RER = respiratory exchange ratio; VE/VCo_2 = exercise ventilation/carbon dioxide production ratio; other abbreviation as in Table 2.

Table 5 Echocardiographic Parameters

Parameter	Placebo					Ranolazine				
	Baseline	22 h	14 Days	p Value	p Value*	Baseline	22 h	14 Days	p Value	p Value*
LVEDV (ml)	45 ± 4.2	62 ± 13.0	45 ± 3.5	0.31	1.00	72 ± 8.0	68 ± 8.9	78 ± 8.7	0.21	0.63	0.13	0.73
LVEDVI (ml/kg)	26.9 ± 2.6	37.2 ± 7.6	27 ± 2.0	0.31	1.00	40.5 ± 4.4	38.1 ± 4.7	45.3 ± 5.3	0.23	0.70	0.12	0.73
LVESV (ml)	19 ± 2.2	26 ± 7.3	15 ± 3.0	0.69	0.75	26 ± 4.2	26 ± 5.1	30 ± 4.8	0.87	0.51	0.71	0.43
LVESVI (ml/kg)	11.2 ± 1.5	15.4 ± 4.3	8.8 ± 1.8	0.63	0.81	14.2 ± 2.2	14.3 ± 2.7	17 ± 2.9	0.61	0.48	0.79	0.34
LVSV (ml)	26 ± 2.3	37 ± 5.7	31 ± 1.4	0.13	0.13	46 ± 4.2	42 ± 4.2	49 ± 4.3	0.17	0.85	0.03	0.69
LVEF (%)	59 ± 1.5	61 ± 2.2	65 ± 3.6	0.63	0.22	66 ± 2.2	68 ± 3.3	65 ± 2.9	0.91	0.27	0.33	0.03
E (cm/s)	96 ± 3.8	90 ± 3.6	94 ± 7.2	0.38	1.00	100 ± 4.9	96 ± 5.8	93 ± 4.2	0.51	0.41	0.85	0.74
A (cm/s)	92 ± 9.9	88 ± 10.9	87 ± 12.9	0.16	0.69	88 ± 9.7	85 ± 9.6	87 ± 11.3	0.42	0.13	0.67	0.82
E/A	1.1 ± 0.1	1.2 ± 0.2	1.4 ± 0.3	0.56	0.69	1.4 ± 0.2	1.5 ± 0.3	1.5 ± 0.3	0.77	0.39	0.77	0.93
E′ (cm/s)	5.93 ± 0.9	6.36 ± 1.2	5.98 ± 1.1	0.84	0.84	5.5 ± 0.5	5.83 ± 0.6	5.34 ± 0.4	0.52	0.52	1.00	0.41
E/E′	18.3 ± 2.3	18.4 ± 3.5	18.8 ± 0.3	0.74	0.31	19.1 ± 1.0	17.6 ± 1.3	18.3 ± 0.7	0.47	0.70	0.85	0.56

Values are mean ± SEM. p Values compare baseline versus 22-h values. *p Values compare baseline versus 14-day values. Plac vs. Ran is a comparison of 22-day values, and *p Plac vs. Ran is a comparison of 14-day values.
A = mitral A-wave velocity; E = mitral E-wave velocity; E′ = mitral annular velocity; LVEDV = left ventricular end-diastolic volume; LVEDVI = left ventricular end-diastolic volume index (normalized to body weight); LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVESVI = left ventricular end-systolic volume index (normalized to body weight); LVSV = left ventricular stroke volume.

Discussion

Results of this proof-of-concept study showed that ranolazine given intravenously for 24 h in patients with HFpEF was safe and modestly improved some important measures of diastolic function with decreases in LVEDP and PCWP during resting conditions and decrease in mPAP during paced conditions. After 14 days of oral treatment, no significant changes in noninvasive measures for diastolic function were observed.

Preclinical and clinical evidence for altered handling of Ca^{2+} and Na^{+} in diastolic dysfunction. Ranolazine, a potent late I_{Na} inhibitor, may normalize altered intracellular Ca^{2+} concentration due to the close relationship between Na^{+} and Ca^{2+} handling by the Na^{+}/Ca^{2+} exchanger. Until now, ranolazine has been clinically investigated only as an antianginal agent in patients with coronary artery disease (21–23).

In vivo experiments suggest that late I_{Na} inhibition may be a potential therapeutic approach to improving diastolic function, but no placebo-controlled study has been performed (17).

In the MERLIN–TIMI-36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndromes–Thrombolysis In Myocardial Infarction-36) trial, patients with acute coronary syndrome treated with ranolazine showed a significant improvement in the combined primary endpoint (cardiovascular death,

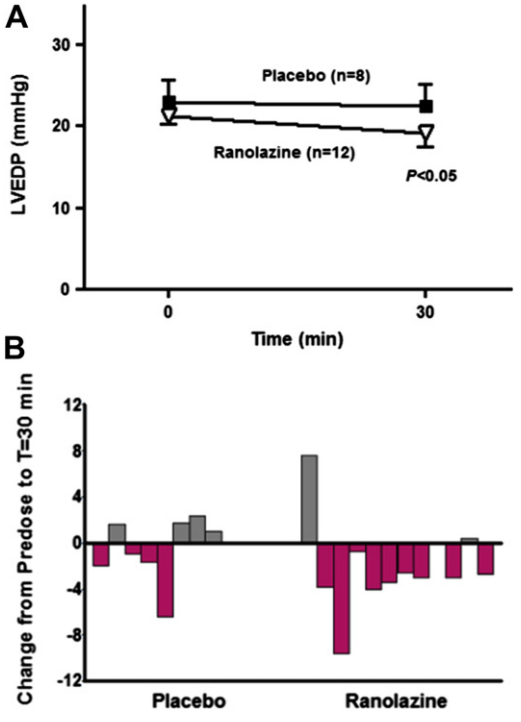

Figure 2 Acute Effects of Ranolzine on LVEDP

(A) Acute effects of ranolazine (n = 12) versus placebo (n = 8) on average left ventricular end-diastolic pressure (LVEDP) before and after intravenous infusion. **(B)** Individual responses of changes in LVEDP.

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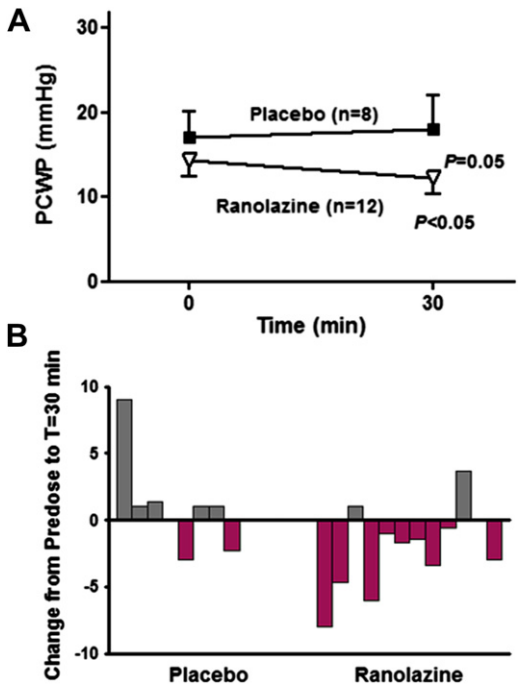

Figure 3 Acute Effects of Ranolazine on PCWP

(A) Acute effects of ranolazine (n = 12) versus placebo (n = 8) on pulmonary capillary wedge pressure (PCWP) before and after intravenous infusion, during basal conditions (at rest). **(B)** Individual responses of changes in PCWP.

myocardial infarction, recurrent ischemia) if BNP levels were elevated (24). Because BNP levels are known to be indicative of increased wall tension, the beneficial effects of ranolazine in this group of patients may suggest an improvement of wall stress and diastolic function.

Acute ranolazine effects. The present data with immediate, although modest, improvements in LVEDP, PCWP, and mPAP in the presence of ranolazine suggest the potential role of late I_{Na} inhibition in the treatment of diastolic dysfunction. Of interest, these findings occurred with unchanged pulmonary and systemic resistance, which makes pure vasodilation as the underlying mechanism for the decrease in filling pressures rather unlikely. However, whether the small changes in pressure of ~2 mm Hg in the presence of ranolazine actually may have any clinical relevance remains to be determined in a larger trial.

Hemodynamic relaxation kinetics (e.g., dP/dt_{min} and tau) were not affected by ranolazine. This finding is consistent with a recent in vitro report showing a lack of an improvement by ranolazine in active relaxation, although diastolic dysfunction over time was improved (15). Mechanistically, in diastolic HF there seems to be a difference between passive (or late-phase) relaxation, which may well be related to diastolic tension, and hence, improved by ranolazine due to improvement in slow Na^+-dependent Ca^{2+} overload, and active (or early) relaxation, which would be more related to sarcoplasmic reticulum reuptake of Ca^{2+} ions from beat to beat, and, hence would not be affected by ranolazine.

A report of 5 patients with LQT3 syndrome showed that ranolazine caused an improvement in relaxation (25). This discrepancy may be the result of differences in levels of late I_{Na} and its relative contribution to ventricular repolarization/relaxation in different diseases. Hence, the magnitude of the reduction in late I_{Na} (estimated by changes in QTc) by ranolazine was much larger with a mean QTc shortening of 26.3 ± 3.5 ms, whereas in the present study of HFpEF patients, no QT shortening was observed.

Pulmonary hypertension (PH) is highly prevalent and often severe in HFpEF and is associated with increased mortality (26). Although a precapillary component is frequent in PH and HFpEF, there are concerns regarding the use of pulmonary vasodilators because increasing right heart output may result in further increases in left atrial pressures (27). In this study, ranolazine decreased mPAP without effects on PVR. Baseline mPAP was 24.4 mm Hg in the ranolazine group and 28.7 mm Hg in the placebo group, indicating a mild PH. It might be speculated whether, in HFpEF and

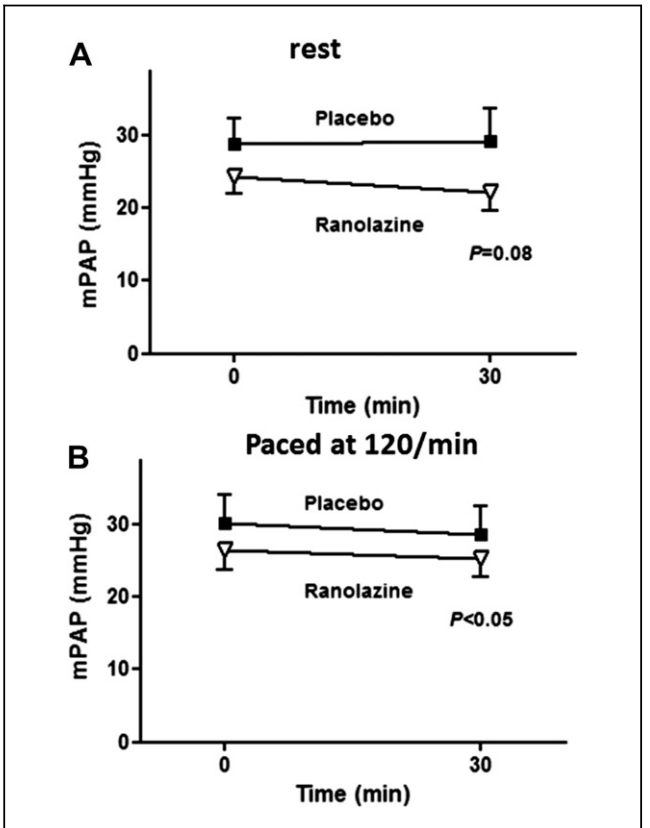

Figure 4 Acute Effects of Ranolazine on mPAP

(A) Acute effects of ranolazine (n = 12) versus placebo (n = 8) on mean pulmonary arterial pressure (mPAP) before and after intravenous infusion during basal conditions (at rest). **(B)** Acute effects of ranolazine (n = 12) versus placebo (n = 8) on mPAP before and after intravenous infusion when pacing at 120 beats/min.

Table 6 Effects on Blood Pressure and Heart Rate

Hemodynamic Values	Placebo	Ranolazine	p Value
SBP screening on day 0 (mm Hg)	133 ± 8	142 ± 8	
SBP on day 14 (mm Hg)	130 ± 8	135 ± 8	0.594
DBP screening on day 0 (mm Hg)	78 ± 4	73 ± 3	
DBP on day 14 (mm Hg)	74 ± 4	71 ± 3	0.858
Heart rate on screening day 0 (beats/min)	72 ± 3	64 ± 4	
Heart rate on day 14 (beats/min)	74 ± 4	65 ± 3	0.934

Values are mean ± SEM.
DBP = diastolic blood pressure; SBP = systolic blood pressure.

severe PH, the effect of ranolazine on mPAP would be more pronounced.

Cardiac output, dP/dt_{max}, and stroke volume decreased slightly in the presence of ranolazine, indicating an acute reduction of systolic function. This is in line with in vitro observations demonstrating a mild negative inotropic effect of ranolazine (15). One explanation may be that ranolazine reduces intracellular Na^+ and Ca^{2+} levels and hence reduces actin/myofilament interaction. A recent finding suggests that ranolazine causes a small decrease in myofilament Ca^{2+} sensitivity in a mouse model of diastolic dysfunction (28). Whether the changes in dP/dt_{max} and stroke volume are clinically relevant is speculative, but it is possible that these effects may offset the positive effects on diastolic function. Nevertheless, systolic blood pressure and EF remained unaffected throughout the study. In this regard, it should be noted that even beta-blockers acutely exert negative inotropic effects but improve systolic function and prognosis over time in patients with SHF (29). Hence, a small negative acute reduction in inotropy does not preclude positive long-term results in HF.

Effects of ranolazine after 14 days. After 14 days of treatment, we did not see any significant changes in echocardiographic and CPET data. The number and severity of adverse events were similar in both groups. Therefore, within the range of the limited number of study participants in the RALI-DHF study, ranolazine can safely be applied in HFpEF.

Table 7 Effects on Repolarization Measures as QT Interval in the ECG

Parameter	Placebo (n = 8)	Ranolazine (n = 12)	p Value†
QT interval (ms)*			
Baseline	410 ± 9	413 ± 9	
End of infusion	400 ± 11	431 ± 10	0.06
Day 14	403 ± 11	422 ± 11	0.20
QTcB (ms)			
Baseline	424 ± 6	421 ± 7	
End of infusion	427 ± 6	448 ± 10	0.21
Day 14	439 ± 5	428 ± 9	0.70
QTcF (ms)			
Baseline	419 ± 4	418 ± 7	
End of infusion	418 ± 7	442 ± 8	0.13
Day 14	426 ± 7	426 ± 9	0.82

Values are mean ± SEM. *The QT interval was corrected for heart rate using Bazett's (QTcB) and Fridericia's (QTcF) formulas. †p Value from Wilcoxon rank sum test on change from baseline values between ranolazine and placebo groups.
QTcB = corrected QT interval after Bazett's formula; QTcF = corrected QT interval after Fridericia's formula.

Study limitations. An abnormal handling of Ca^{2+} and Na^+ is only one of several factors contributing to diastolic HF. Increased interstitial deposition of collagen and modified matricellular proteins also contribute to increased myocardial stiffness and slowed LV relaxation (30). Tau and other parameters for relaxation (e.g., t relax [time of relaxation], t sys [time in systole], and t dias [time in diastole]) were unaltered in this study and were markedly higher than those in a previous study, indicating severe diastolic HF in patients of the current study (20). Thus, a short-term treatment of ranolazine (acutely and up to 14 days) is not sufficient to affect the structural pathophysiology, and therefore, may be too short to detect beneficial effects in noninvasive parameters.

Also, we are aware of discrepancies between previous invasive positive proof-of-concept reports and several subsequent negative clinical trials and thereby acknowledge that there is no evidence that changes induced acutely by ranolazine would be predictive of the long-term beneficial effects.

The RALI-DHF study is considered exploratory, and therefore, there is no statistical justification for the present sample size. Post hoc analysis with power calculations assuming a two-sided alpha of 0.05 and a 1:1 randomization suggested a 39% power for LVEDP, 75% for PCWP, and 70% for mPAP when including 40 patients instead of 20 patients (currently 21%, 44%, and 40%, respectively).

Finally, we have to acknowledge that some of the significant results of this study could have been the results of chance because of the small number of patients studied and the multiple hypotheses tested.

Conclusions

Results of this proof-of-concept study revealed that ranolazine improved measures of hemodynamics, but that there was no improvement in relaxation parameters.

Reprint requests and correspondence: Dr. Lars S. Maier, Department of Cardiology and Pneumology, Heart Center/Georg-August-University Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany. E-mail: lmaier@med.uni-goettingen.de.

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Key Words: diastolic dysfunction ■ heart failure with preserved ejection fraction ■ late I_{Na} inhibition.

APPENDIX

For an expanded Methods section and a supplemental table, please see the online version of this article.